APIC Active Pharmaceutical Ingredients Committee

To secure API supply for Generic Market in Japan through a “Post approval change guidance”

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Post approval change registration guidance

- The purpose of a **"Post approval change registration guidance"** is to define clear rules and identify the supportive data to guarantee that the change proposed by the manufacturer doesn't affect the quality, efficacy of the product and the safety of patient compared to what is described in the approved dossier.

- This type of guidance per country or per zone is a very useful tool for manufacturers to anticipate the regulatory impact of the proposed change worldwide and to plan how it can be managed taking into consideration all constraints:
  e.g. ***Health Authorities requirements for each country, equipment availability, additional laboratory investigations to perform, resources and cost.***

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Post approval change registration guidance

- Basically, in Japan **Generic DP dossiers only make a cross-reference to Manufacturing process section of JMF**. A guide on the maintenance of this section is defined in the Japanese regulation.

- For Specifications & Tests section, it is not so clear for manufacturers. We use more and more **"Simple consultation procedure"** which is very appreciated and useful but the provided decision is explicitly **only for one special case**.

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Post approval change registration guidance

- **APIC suggestion**:
  Would it be possible to complete this JP guidance for Specifications and Tests section?

For each category of proposed change: ***Manufacture, Control of active substance, Container closure system, Stability,*** it is key to know the :

- Conditions to be fulfilled
- Documentation to be supplied
- Procedure type: MCN, PCA

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Post approval change registration guidance

- The existing JP guideline for Manufacturing process section of JMF **is not consistent with existing guidances from ICH member states.**
  - In Japan, **a major change** (**PCA**) needs before any approval around **12 months in practice.**
  - In most of the cases a **process change** even at early step in the chemical synthesis is assessed as a major change in Japan compared to minor change or annually reportable in European and US regulations.

- **Reclassification of some process changes to minor ones** would mitigate the regulatory burden when final quality of the API is not impacted as it is currently in place in Europe and US.

Post approval change registration guidance

APIC suggestion:

"Simple consultation" procedure is in place for more than 10 years, but more frequently used by European API manufacturers from last year.

Would it be possible to list some general cases by consolidating at least one year of results from the decisions of simple consultations?

It would be very helpful to publish this list of typical cases.

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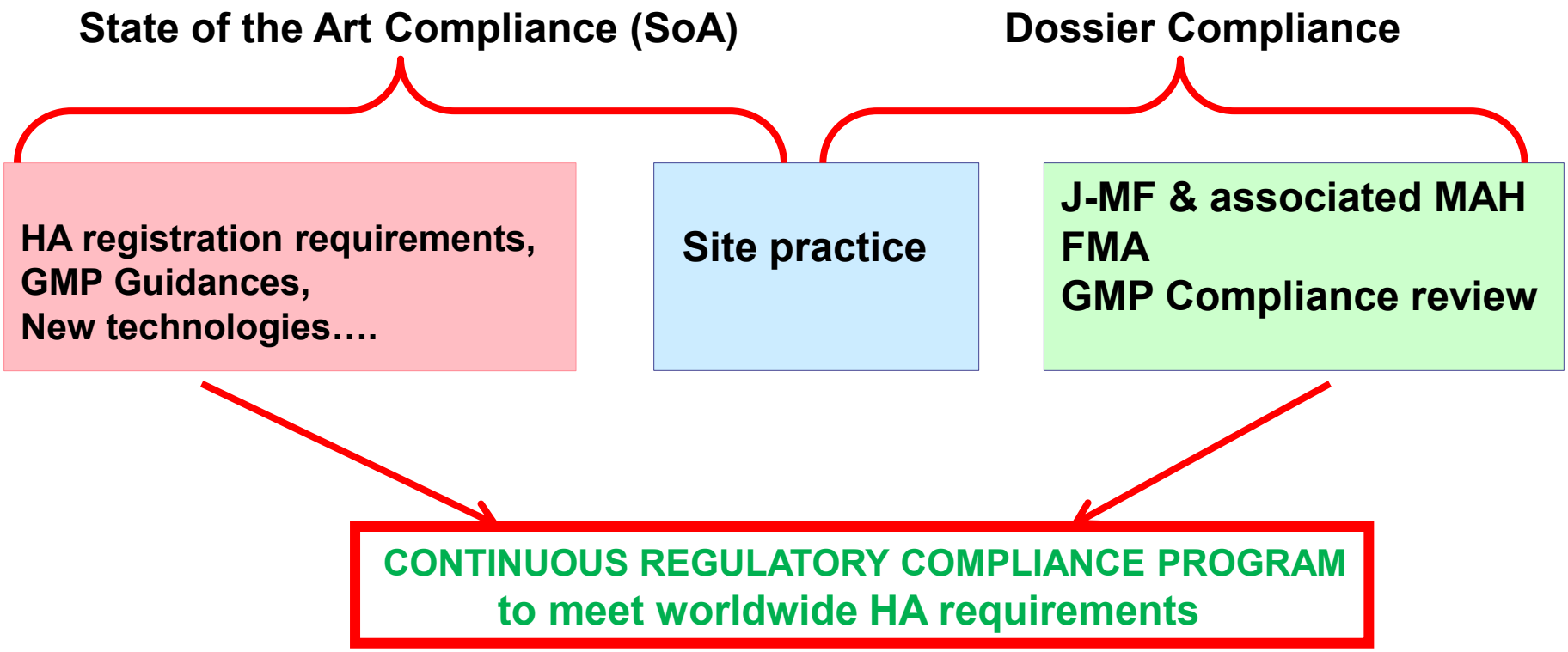
High challenge on Regulatory Compliance for Manufacturers



HA: Health Authorities MAH: Marketing Authorization Holder FMA: Foreign Manufacturer Accreditation

Regulatory Compliance status

- **“Dossiers non compliance” due to the very specific JP dossier format & rules not consistent with CTD format (ICH):**

  Some regulatory burden could be avoided further discrepancies observed by PMDA between:

  - **Module1 & Module3 after minor change notification (MCN)**

- In case of minor change only Module1 will be amended according JP rule. Amendment of Module 2 is not clear.
- Consequently, the API manufacturer will be declared systematically “Non compliant” during the next GMP Compliance review

Regulatory Compliance status

- **"Dossiers non compliance" due to the very specific JP dossier format & rules not consistent with the site practice:**

  Some regulatory burden could be avoided further GMP compliance review and discrepancies observed by PMDA between:

  - **Master Batch Record (MBR)/ Module1/ Module3**

  Examples:

  - **Process parameters as a range in MBR and a set value in the Module 1.**
  - **Systematic critical parameters in the process as a basic rule in a J-MF.**
  - **Monitoring parameters are not critical when no impact on the quality.**
  - **Module 1 is not a copy paste of MBR. It is "normal" that additional details are included in the worksheets. MBR is the tool of the operator at workshop and done to make him comfortable with the process.**

Regulatory Compliance status

- **"Dossier non compliance" due to miswriting and mistranslation:**
  - **MHLW notifications dated in 2016 (January19th & February 12th)** give us a good chance to correct discrepancies.
  - Although we are doing our best to correct discrepancies, human errors happen. Many actors interfere. High risk of misinterpretation **(cultural approach, English translation)**. CTD format allows a direct contact between manufacturer and PMDA.

- **APIC suggestion:**

If discrepancies do not have any impact on quality, efficacy, safety would it be possible to adapt JP regulation allowing manufacturers to proceed through easier regulatory actions and amend existing dossiers with a Minor impact (MCN) or through Annual Report ?

To take more in consideration module3 to limit technical misunderstanding.

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Conclusion

- **Regulatory burden** should be mitigated when API quality is not impacted especially in the context of post approval change registration dossiers.
- No compromises when patient safety is at stake.
- Stable supply is also key to protect public health.
- Reinforced collaboration between Industry & Health Authorities based on a better understanding of mutual constraints could help to improve the efficiency of the Regulatory Procedure.